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synapse

Bishop and Varmus win the Nobel Prize

On the eve of its 125th birthday celebration —which is partly intended to remind the world that some good and significant work goes on here— UCSF got the gift of a lifetime as professors J. Michael Bishop and Harold E. Varmus were awarded the 1989 Nobel Prize in medicine.

It was in 1976 that Varmus and Bishop first reported that certain genes which occur normally in all vertebrates may function as switches that set off malignant growth in response to various carcinogenic insults. Some 50 of these "proto-oncogenes" have now been identified by numerous investigators.

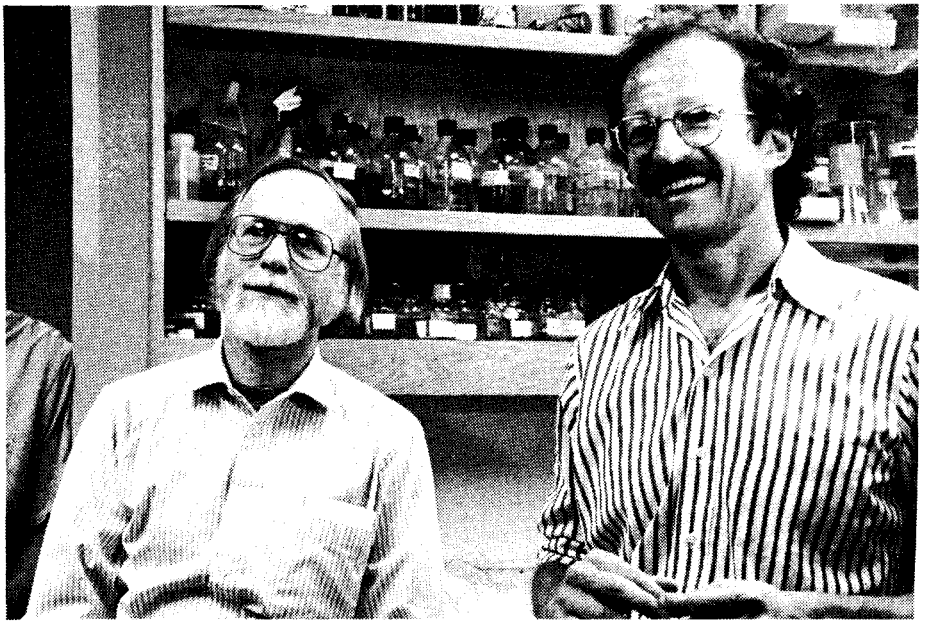
Their original finding --which preceded advances in biotechnology that have made such experimentation relatively straightforward-- implied that there is a unifying explanation of how most or all cancers arise.

UCSF's first-ever Nobel laureates are both professors of microbiology, biochemistry and biophysics, and are widely regarded by students as lucid and friendly teachers. Each now directs a group of some 20 co-workers, post-doctoral scholars and graduate students carrying on research that stems from their earlier collaborations. Bishop is also director of the George W. Hooper Research Foundation and Varmus is American Cancer Society Professor of Molecular Virology.

News of the honor —which includes a $469,000 cash award the two will share— reached Bishop and Varmus in the wee, small hours of Monday, Oct. 9. By 8:30 a.m. they were facing reporters and camera persons in the Chancellor's Conference Room as a crowd of smiling colleagues and friends spilled into the adjoining hallways.

What follows is an edited transcript of that press conference.

--Fred Gardner



J. Michael Bishop and Harold E. Varmus, Oct. 9, 1989. *Photo by Monty Dunn.*

Q: It was known that you were in the running, but even so, when you got the call today was it a surprise to hear that you'd won the Nobel Prize?

B: For me it was frightening because my 17-year-old son took the call. The phone in our bedroom doesn't work —on purpose— and he came into our bedroom at about 3:30 and woke us up and we just assumed that one of the grandparents had some trouble, so I was frightened. He said "Don't worry, Dad, it's NBC with good news."

Q: What was your initial reaction?

V: Needless to say, I was surprised. You may know you're in the running, but nevertheless there are a lot of other good people that are, too. The actual recognition is a moment when you pull back and say "Jesus, why isn't it the other people?" And it's a shock.

Q: Can you explain in brief what it is your work is and what your direction was?

V to B: Want to take that one?

B: The idea has been around for a long time that cancer is a genetic disease, that cancer cells happen because something goes wrong with the genetic machinery that runs our cells. This doesn't mean that it's always inherited. Genes run our cells from the day we're born to the day we die, so the idea has been that something happens to those genes —they get damaged and cause cells to run amuck. What our work did was to help give substance to that idea by showing that one —and indeed now dozens of genes from our cells— can indeed become cancer genes if they're damaged. We found this to be true first in a virus that had gotten the gene from cells by piracy. It's now been shown in many other ways, so to rephrase that, our work gave substance to the idea that our cells contain genes that if damaged, can give rise to cancerous growth. So, if you will, we have the seeds of cancer in our own genetic dowry.

Q: Are we speaking about all types of cancer?

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B: Potentially; or many. We couldn't say yet.

V: The work began with a virus of chickens, a virus which incidentally, was discovered in 1910 by a man named Peyton Rous who won the Nobel Prize for that discovery in 1966. The challenge to us was to ask what it is about that virus which makes it a cancer virus? And work by several other laboratories, Steven Martin at Berkeley and Peter Vogt at the University of Southern California and Hidesaburo Hanafusa at Rockefeller University, showed that there was a single gene in that virus that was responsible for the tumor-causing ability of the virus. Work that was done in our laboratory by Dominique Stehelin and other postdoctoral follows, showed that this gene was actually, although in a virus, derived from a normal cellular gene.

Q: It's been 13 years since the paper came our first identifying this gene. Have you seen the fruits of your work furthered in those years? Have you seen practical application in human cancer fighting?

B: Well, we've seen a blizzard of work. I was tempted to answer the question about whether I was surprised, by saying "Yes indeed," because since our initial discovery there has been so much else done that, in a sense, what we did has been buried in a remarkable series of discoveries that show that in many different forms of human cancer the kinds of genes we first came upon are indeed damaged, and indeed seem to contribute to the genesis of human cancer. So there are many people out there who have made contributions to this field, not only before as Harold mentioned, but since. So I was beginning to think that we'd gotten lost in the blizzard.

Q: Is there any therapeutic application down the road?

V: Only if you look way down the road in the sense that if you want to understand cancer you need to know the genetic players in the causation of cancer. The initial challenge is in identifying those players. The next challenge is understanding how those genetic players actually work at a biochemical level —what kind of proteins they make, what those proteins do— and in that way try to devise biochemical strategies for interfering with the action of those proteins. That's where the main challenge lies now in the field of oncological research: to understand how so-called cancer-causing proteins actually carry out their activities.

Q: Has there been a personal thing that got you involved in this work, friends, family, is there something in your heart as well as in your head that...?

V: Well, I hope there's something in our hearts as well as in our heads (laughs)... My mother died of breast cancer but I don't know if that itself is what impels you to study the problem. You think the problem is important, potentially interesting, there are ways to go about it technically, and that's what drives you. There's hardly anybody in this room who is not touched by cancer in some way.

Q: What are you working on now? And are you working together as a team?

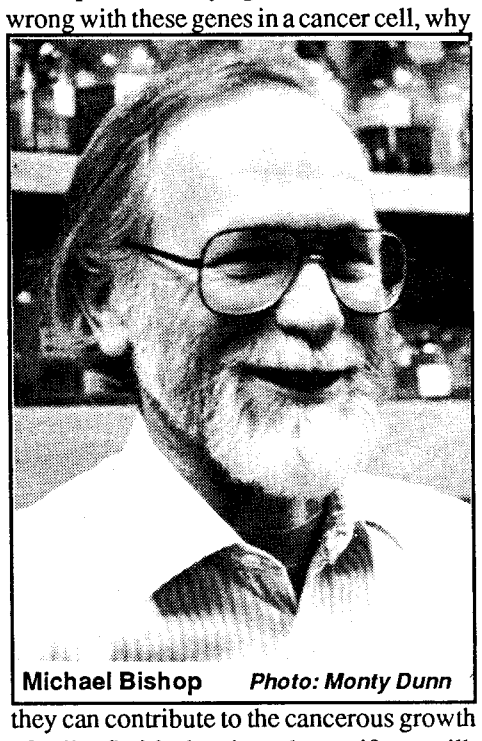
V: We no longer share one laboratory, we have separate laboratories, but we do collaborate on several things. My lab works half on the manner in which retroviruses— the viruses typified by the Rous sarcoma virus and the AIDS virus— the way those viruses grow. It's not necessarily a cancer problem but a problem of the mechanism of virus growth and its implications for understanding many diseases caused by retroviruses, including AIDS. The other half of our laboratory works on some of the biochemical aspects of a couple of the oncogenes we've been involved with over the years.

Q: How close does this bring us to a cure which the whole world is waiting for?

B: That's an imponderable at the moment. But we certainly have a better image of what is wrong with the cancer cell than we did 10 years ago and that's a step in the right direction. You have to understand the machine if you're ever going to be able to fix it.

Q: Can you explain what you (Bishop) are working on now?

B: Yes. The original finding has lead in two directions. The one that's been focused on here: what's wrong with cancer cells? And the other is that by finding this sort of gene in cells, we've come upon genes that are vital to the normal activities of cells, to the everyday lives of cells. These genes were not put there to cause cancer as Harold once put it to Time Magazine as I recall, they were put there for other reasons. They were put there to conduct the normal affairs of cells. In that sense it's a gold mine, to have access to some of the genetic apparatus that runs our cells in our normal activities, as well as sometimes go awry in cancer cells. We're trying to understand what some of these genes do for the normal cell in growth and development, and trying to understand what's wrong with these genes in a cancer cell, why



Michael Bishop *Photo: Monty Dunn*

they can contribute to the cancerous growth of cells. So it's the yin and yang if you will, the normal and the abnormal. We try to balance these two. Basically, we try to make experiments work from month to month.

Q: How does it feel to win the Nobel Prize?

B: Surreal.

Q: How will the prize affect your future?

B: I hope it has no impact whatsoever.

V: It's probably illusory, but I like my life the way it is and I hope it stays that way.

Q: Do you feel you have more to live up to now that you've been recognized?

V: The danger is that you're supposed to be smarter today than you were yesterday, and I'm not.

Q: Will this make it easier to get research money now that you've won the prize?

B: I doubt that very much. (General laughter.)

Q: Was this research you were doing unique to you gentlemen, or were others working on the same project?

V: Now, of course, there are thousands working on similar things. At the time there were many people working on related problems. It's a matter of timing, choosing the right reagents, making the experiment the most credible. We were obviously challenging hypotheses that already existed, using reagents that others had provided. We all stand on the shoulders of those who come before us. The field is complex and many have made very important discoveries in the field of oncogenes who were unfortunately ignored on this occasion.

B: I think one of the things that distinguished this work is that it came before recombinant DNA, and it was brutally difficult technically. So we have to give great credit to Dominique Stehelin, who actually carried out the bulk of the experiments. These were extremely demanding experiments and the fact that he got them to work is probably one of the things that distinguishes this work in its time and place, because they were extremely difficult without what eventually became straightforward with molecular cloning.

Q: Why did Stehelin get his name on the first paper and yet was not recognized by the committee? Can you explain how that works?

B: He was a postdoctoral fellow at the time, executing experiments that Harold and I had conceived. This is an issue that's debated every year almost, and it has to be left to the Nobel Committee to make those decisions.

Q: He was the experimentalist and you folks were the theoreticians?

B: We were both at the bench yet at that time... (laughter) but he did the particular experiments reported in that paper.

Q: Who is Peter Vogt? What was his role and was he a coauthor?

B: He had isolated the particular strain of virus that made it possible to do these experiments. We felt that that contribution was so strong and his generosity was so great, that he had to be a co-author. As I recall he disputed this at first, but he belonged there.

V: One of the things that distingushed the work in question is the genetic purity of the experiment, if you'll excuse the expression. That is, we were working with what is still the sole retrovirus that can both grow and cause tumors without the requirement of an additional virus as a helper. And this meant that you could make mutations in the cancer-causing gene —mutations in the genes required for multiplication of the virus— independently. And this was a crucial aspect of the experiments. We are indebted to Peter Vogt for having isolated the appropriate mutants that allowed us to do the work that Stehelin carried out.

It should also be pointed out that, in addition to Stehelin, there were others involved in the series of experiments in question, not with the paper that you're citing, but there were a series of papers that involved the molecular reagents and preparations, the tools that were used to carry out the experiments, and the follow-ups of many kinds that were required to show that the gene in question was in fact a cellular gene from which the viral oncogene was derived.

Q: Before your work, what was the prevailing theory of tumor genesis?

V: Well, there have been many theories. What was heuristically most important to us was the theory first espoused by George Todaro and Robert Huebner called the oncogene and viral gene hypothesis, which was based on the idea that all normal cells had copies of viral chromosomes, viral genes. This was based on evidence that in fact genes that are involved in the multiplication of viruses were in fact present (and are now known to be present) in the chromosomes of all of us from chickens to man. The extrapolation of the hypothesis was that those viral gene collections contained within them a viral oncogene and that that was indigenous to man and could be activated by a variety of carcinogenic insults, chemical, radiation and so forth. Our work was addressed initially to challenging that hypothesis, asking: is it true that there are oncogenes in normal cells? And secondly, if so, are those genes part of viral units or are they cellular genes but a more generic type. And what our work showed over the next few years was that in fact the latter was true. These genes were garden variety cellular genes that are normally involved in making us all the interesting, complex organisms that we are, but are sometimes misdirected by mutations.

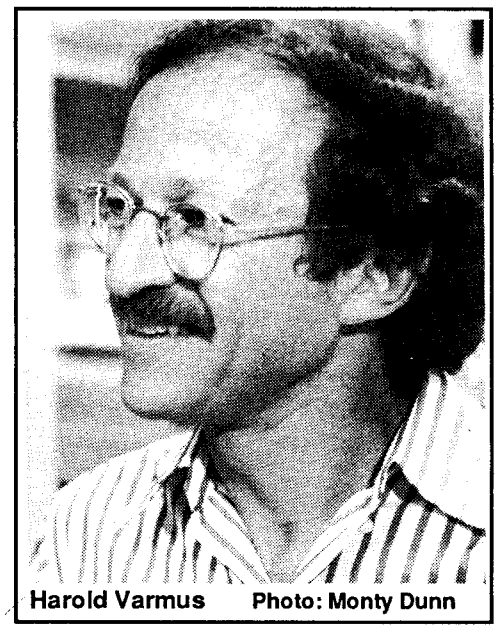
Q: Do you know if they are dormant genes that only get triggered when a virus comes in, or whether they have a function that is somehow transformed when the virus attacks?

B: Well, as I said before, they are all genes that have vital functions for normal cells, they wouldn't have survived the eons of evolution otherwise. (Identifying) those normal functions are one of the two objectives of our research. A dormant gene is a dead gene and will get lost quickly through the course of evolution. These are active and important genes in our cells...

V: (Responding to same question) Think about the term 'latent.' There are genes that are quiet in some cell types and active in others and such genes can be turned on, for example, when a virus introduces a regulatory element next to the gene and by being expressed in an inappropriate place can induce a tumor in that inappropriate place. Other genes may be active in virtually all cells and only play a role in cancer when a mutation occurs that alters the biochemical function of the protein that that gene encodes.

Q: How about a specific example?

V: Sure. The *src* gene—the gene we were working with initially in Rous sarcoma virus— is expressed virtually everywhere, and yet the *src* gene only seems to be a cancer-causing gene when there's a mutation that



Harold Varmus **Photo: Monty Dunn**

affects the biochemical property.

Q: What is the *src* gene?

B: A few years after we made this initial discovery, another one of these genes was being studied. It turned out to be the same, it was an oncogene with its cellular progenitor. And it was discovered that the progenitor was the gene that encoded the epidermal growth factor, whose discovery earned Stan Cohen a Nobel Prize several years ago.

Q: It causes skin to grow?

B: Exactly. It is also a gene that can be perverted into an oncogene.

Q: What kind of cancer does it cause?

B: We couldn't answer that question, we only know that it's been implicated in a number.

Q: Does this make it easier to detect cancer at an earlier stage, since we now have a better understanding of the developmental process?

B: I think that there are some hints of that, that eventually it will be possible to test polyps of the colon for example, but that's a very, very speculative answer,.

V: It's possible to link some of the work that's been done on oncogenes with a major technical development you may have heard about called the polymerase chain reaction, which allows one to look at individual genes in a very small number of cells. That kind of technology could be applied to look for specific mutations if you know ahead of time what kind of mutations and which mutant oncogenes to look for. The other practical application so far is to improve the staging of tumors that are already detected. For example to look in a certain tumor type for a certain kind of mutation that you know is associated with a more advanced stage of a certain kind of cancer, and that's been possible now in at least a couple of instances.

Q: Did you feel [your experiment] was a momentous event?

B: You bet. I was astonished. I didn't think the experiment was going to work. I thought we'd get the opposite from what we got.

V: We thought it was important, I'm told by colleagues that there were many out there who were disbelieving at the time. I don't know if that's true or not.

Q: Do you feel deserving of the award?

B: I answered that question before when I talked about the number of contributions that have occurred before and after. I think, usually —not always but usually— this kind of recognition arises from being in the right time, being in the right place and knowing the right people. I'm pleased and grateful for the recognition, but I know that there are other people out there who have made equivalent contributions. This is a particularly difficult field to sort out in this regard. There has been so much done in the last 10 to 15 years of such impact.

Q: Does being in San Francisco or UC specifically help your research, and what attracted you here?

V: UCSF has been a nurturing environment, there's no doubt about it. One of the great

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things about the place is the collegiality among the faculty and the strong support we get from each other. So it has been a wonderful place to work. Postdocs like coming here because it's a pleasant place to live and we get good postdoctoral applicants, that's always a step in the right direction. We have very smart graduate students in our labs, all these things help move things along.

B: I would like to reiterate my gratitude to the institution. It's been remarkably supportive of me from the day I arrived here, from the top of the administration to the bottom. This is a splendid place to work and the people of San Francisco should be very proud of it.

Q: How long have you been working together?

V: Since 1970.

Q: How long have you been here?

B: I've been here since 1968. It's the only job I've ever had besides putting on roofs in high school.

Q: How did you get to know each other?

B: He walked through my office door one day and said he'd like to work in the lab. And judging from the length of his beard I figured he was probably a free spirit who would do well.

V: ...I ambled into the fourth floor and met Mike and Leon (Levintow) and Warren Levinson, a happy triumvirate up there, and that was the beginning of everything.

Q: Are you going back to work today?

B: I'm going out to see the Giants beat the Cubs and so is Harold. (Wild cheering.)

Q: What is your scientific thinking on the Giants' chances?

B: It all depends on Big Daddy.